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Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas

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✓ Malignant gliomas have been difficult to treat with chemotherapy. The most effective agent, BCNU (carmustine), has considerable systemic toxicity and a short half-life in serum. To obviate these problems, a method has been developed for the local sustained release of chemotherapeutic agents by their incorporation into biodegradable polymers. Implantation of the drug-impregnated polymer at the tumor site allows prolonged local exposure with minimal systemic exposure. In this Phase I-II study, 21 patients with recurrent malignant glioma were treated with BCNU released interstitially by means of a polyanhydride biodegradable polymer implant. Up to eight polymer wafers were placed in the resection cavity intraoperatively, upon completion of tumor debulking. The polymer releases the therapeutic drug for approximately 3 weeks.

Three increasing concentrations of BCNU were studied; the treatment was well tolerated at all three levels. There were no adverse reactions to the BCNU wafer treatment itself. The average survival period after reoperation was 65 weeks for the first dose group, 64 weeks for the second dose group, and 32 weeks for the highest dose group. The overall mean survival time was 48 weeks from reoperation and 94 weeks from the original operation. The overall median survival times were 46 weeks postimplant and 87 weeks from initial surgery. Eighteen (86%) of 21 patients lived more than 1 year from the time of their initial diagnosis and eight (38%) of 21 patients lived more than 1 year after intracranial implantation of the polymer. Frequent hematology, blood chemistry, and urinalysis tests did not reveal any systemic effect from this interstitial chemotherapy.

Since the therapy is well tolerated and safe, a placebo-controlled clinical trial has been started. The trial will measure the effect of the second treatment dose on survival of patients with recurrent malignant glioma.

KEY WORDS • chemotherapy • brain neoplasm • glioma • BCNU • biodegradable polymer • drug delivery

MALIGNANT gliomas, which account for about one-half of the 9000 new cases of primary brain tumors reported in the United States each year, remain refractory to treatment despite numerous attempts to provide effective forms of therapy.[20] The tumors progress rapidly and resection followed by external beam irradiation, the standard treatment, provides median survival times of less than 1 year after surgery.[20] Although some improvement in the number of long-term survivors has been obtained by administration of the nitrosourea BCNU (carmustine), its use has been limited by the systemic toxicity of the drug. Moreover, BCNU has a serum half-life ($T_{\frac{1}{2}}$) of only 15 minutes, further limiting its usefulness.[25] For these reasons, we sought a different means of supplying the drug more directly to the tumor. In this regard, we took advantage of the observation that recurrence of these tumors is usually observed within 2 cm of the initial tumor margin.[17] We therefore developed a biodegradable polymer as a suitable vehicle for incorporating various chemotherapeutic agents and delivering them directly to the site of the tumor.

The polymer consists of polycarboxyphenoxypropane (PCPP) and sebacic acid (SA) in a ratio of 20:80 and can be produced in a variety of forms (including sheets, microspheres, and rods).[3,9-13,22-24,26,27] The BCNU can be incorporated into the matrix, which is hydrophobic, and hence the active agent is protected from hydrolysis. In preclinical studies we showed: first, that PCPP-SA was biocompatible and could be implanted safely in the brain of rodents and primates;[5,6,31] second, that BCNU could be released in a sustained controlled manner;[14,34] and third, that there is significant diffusion of "active BCNU" released from polymers[14,34] and that this form of delivery could inhibit the growth of an experimental malignant glioma in rats.[4,7] Based on these results, we proceeded with a Phase I trial.

We describe here our first study of the administration of BCNU, incorporated into biodegradable polymer wafers, to patients with recurrent tumors. The drug/polymer wafers were implanted at the tumor site after resection of the tumor. The objectives of the study were to determine the safety of increasing doses of BCNU with the polymer in such patients and to establish the feasibility of this novel form of treatment.

Clinical Material and Methods

Patient Population

Patients with recurrent malignant glioma, verified by imaging scans and clinical evaluation, were candidates for enrollment in the study. The inclusion criteria were: an indication for reoperation, that is, the presence of a unilateral single focus of tumor in the cerebrum showing at least a 1.5-cu cm enhancing volume on computerized tomography (CT) scanning; a Karnofsky Performance Scale (KPS)[19] score of at least 60 (indicating ability to function independently) at the time of enrollment; one course of external beam radiation therapy; and no chemotherapy during the 6 weeks before enrollment. In addition, each surgeon had independently determined that another resection would be in the patient's best interest.

Written informed consent was obtained from all patients. The treatment protocol was approved by the Food and Drug Administration and the appropriate institutional review boards at each study center.

BCNU Wafers

The polyanhydride polymer used in this study was BIODEL polymer, a copolymer of PPCA-SA, prepared in a 20:80 ratio by methods described elsewhere.[3,9-13,22-24,26,27] The polymer and BCNU were co-dissolved in methylene chloride and spray-dried into microspheres with inert gas. These microspheres were pressed into wafers 1.4 cm in diameter and 1.0 mm thick by compression molding, packaged in aluminum foil pouches in a nitrogen atmosphere, and sterilized by 2.2 megarad of gamma irradiation.

Trial Design

All patients underwent baseline examination, KPS score determination, and CT with and without contrast enhancement. A craniotomy was then performed for maximum resection of tumor. A fresh-frozen or squash sample of suspected tumor was sent for histological examination; the pathologist's report of malignant glioma was the final admission criterion for the study. Formalin-sized paraffin-embedded blocks were prepared for formal pathological evaluation and slides were sent to the referee neuropathologist (P.C.B.).

After removal of the tumor, wafers were placed on the resection surface to cover as much tissue as possible. Up to eight wafers were used according to the size of the resection cavity, and overlapping was permitted. Sheets of oxidized regenerated cellulose (Surgicel) were occasionally used to secure the polymers against the brain. After wafer placement, the dura was closed, the craniotomy bone was replaced, and the scalp was closed in a conventional manner.

For assessing toxic effects (local and systemic) of interstitial BCNU release, patients were followed for the first 7 weeks by neurological examination, KPS score determination, hematological and blood chemistry testing, and urinalysis. Contrast-enhanced and noncontrast CT scans or magnetic resonance (MR) images were obtained within 1 to 2 days postoperatively and again at 14 and 49 days.

All brain imaging studies (CT for all but one patient who underwent MR imaging) were reviewed by a referee neuroradiologist. They were analyzed to evaluate tumor size and possible local reactions to the treatment.

Dosages and Administration

The three groups with increasing amounts of BCNU were studied sequentially; when one treatment group had demonstrated tolerance of the treatment, the next drug dosage group was started. A modified Fibonacci scale was used to determine the appropriate increase in dose.[30] For Group 1, 25 μg BCNU/sq mm of polymer (1.93% BCNU loading) yielded 3.85 mg of BCNU/wafer for a maximum dose of 31 mg. For Group 2, 50 μg BCNU/sq mm of polymer (3.85% of BCNU loading) yielded 7.7 mg of BCNU/wafer for a maximum dose of 62 mg. For Group 3, 82.5 μg BCNU/sq mm of polymer (6.35% of BCNU loading) was utilized to yield 12.7 mg BCNU/wafer for a maximum patient dose of 102 mg.

Statistical Methods

Dosage groups were compared with respect to the demographic variables of patient age, weight, and height by use of the Kruskal-Wallis test. The groups were also compared with regard to sex and race, by use of a chi-square contingency table analysis.[35]

The dosage groups were compared by the Kruskal-Wallis test at baseline and at each subsequent visit with respect to a standardized detailed neurological exami-

ation and the KPS score. At each visit, the change from baseline was computed for each patient. Within each treatment group, the significance of this change was determined by the Wilcoxon paired-sample test while the treatment groups were compared by the Kruskal-Wallis test. Survival curves were determined for each treatment group by the Kaplan-Meier method, while the treatment groups were compared by the log rank test (Mantel-Cox) and the generalized Wilcoxon test (Breslow).[35]

The change from baseline data of hematology, blood chemistry, and urinalysis results was computed for each patient. For each treatment group, the significance of the change from baseline at each visit was determined by the Wilcoxon paired-sample test. The treatment groups were compared using the Kruskal-Wallis test. The results were considered to be statistically significant if the two-sided p value was 0.05 or less.

Results

Patients

Twenty-one patients entered the study between September, 1987, and July, 1988. Five patients were treated with 3.85 mg of BCNU/wafer (Group 1), five with 7.7 mg of BCNU/wafer (Group 2), and 11 with 12.7 mg BCNU/wafer (Group 3). Most of the patients received all eight polymer implants.

No significant differences were found among treatment groups for age (average 48.6 years), body weight and height, sex, race, baseline KPS score, or interval since initial surgery (average 46 weeks). In the first two treatment groups, 60% had glioblastomas, whereas all of the patients in the third treatment group initially had glioblastomas. Tumor volumes were not significantly different among treatment groups.

Ten patients had previously received various types of chemotherapy including BCNU, CCNU (lomustine), cisplatin, and alpha-interferon. In addition, one patient from treatment Group 3 had received ^{125}I implants.

Neurological and Karnofsky Examinations

Patients were generally in good condition on enrollment. The mean KPS scores for Groups 1 to 3 were 82, 86, and 82, respectively. Immediately following surgery, most patients showed a drop in both neurological function and KPS score, reflecting the immediate consequences of craniotomy and tumor removal. Within 2 weeks, however, most had improved their neurological and KPS scores to preoperative values and these remained stable through Day 49 of the study, with mean KPS scores for Groups 1 to 3 of 84, 86, and 72, respectively.

A significant difference among treatment groups was found for changes in visual acuity at 14, 28, and 49 days after surgery. Three patients in Group 3, with tumors located in the occipital lobe, had disturbances of vision at baseline examination. These disturbances persisted after surgery, contributing largely to the statistically significant differences observed. No other neurological component and no KPS showed statistically significant differences either within a group (change from baseline values) or between groups.

Laboratory Analyses

No patients had a significant reduction in blood cell counts that would indicate systemic exposure to BCNU. Moreover, blood chemistry and urinalysis did not show evidence of renal or hepatic injury. Hyperglycemia and glycosuria were observed, but these could be attributed to the large amounts of corticosteroid used in treating these patients.

Tumor Imaging

In 13 of the 21 patients (evenly distributed among treatment groups), scans obtained on Days 14 and 49 of the study revealed a distinct thin ring and areas of contrast enhancement. In about one-half of these patients, most of the enhancing effect resolved within 7 weeks; in the other patients it persisted or increased. Clinical and neurological evaluation did not reveal any correlation between the occurrence or development of contrast enhancement and any sign or symptom of toxicity. Thus, despite sometimes marked increases in enhancement, there was minimal net mass effect. Vague outlines of wafers in or near the original placement site could be seen on noncontrast and contrast-enhanced CT scans obtained postoperatively (Fig. 1) and, in some patients, at intervals up to 49 days following surgery.

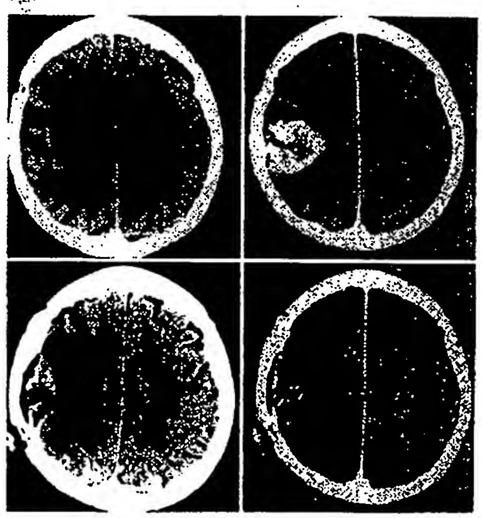

FIG. 1. *Upper:* Preoperative computerized tomography (CT) scans, without *(left)* and with *(right)* contrast enhancement. *Lower:* Postoperative CT scans, without *(left)* and with *(right)* contrast enhancement. Polymer wafers appear as bright white lines along the resected tumor-bed surface.

Survival Period

Mean postimplant survival times for Groups 1, 2, and 3 were at least 65, 64, and 32 weeks, respectively, with median survival times of 65, 47, and 23 weeks, respectively. The overall mean period of survival was 48 weeks from implantation and 94 weeks from the initial operation. The overall median survival times were 46 weeks from implant surgery and 87 weeks from initial surgery. Clinically and radiologically, patients in this series who died had recurrence of tumor or other tumor-related events. At last evaluation (March 1, 1990), two patients were still alive after surviving 109 and 125 weeks. There were no significant differences in period of survival of the four patients with anaplastic astrocytoma as compared to the overall group.

Clinical Events

The expected course of events for postoperative neurosurgical patients was observed and no medical occurrences appeared to result from the polymer implants. Ten patients underwent reoperations during the course of this study: two patients in Group 1; three patients in Group 2, an average of 21 weeks postimplant; and five patients in Group 3, an average of 17 weeks postimplant. Interstitial radioactive seeds were implanted in one Group 1 patient at 68 weeks and in one Group 3 patient at 23 weeks. One patient in Group 1 underwent a contralateral craniotomy for placement of interleukin-2 (IL-2) at 50 weeks after polymer implantation.

The principal finding at reexploration was necrotic tissue, similar to that reported following interstitial radiation treatment. Removal of the necrotic tissue generally proved beneficial.

Eight patients had seizures during the study; all of these had a preexisting tumor-related seizure disorder. All patients experienced cerebral edema during the study, as is typical for postoperative craniotomy patients, and all received postsurgical corticosteroid treatment. There were no significant differences between the three groups regarding steroid requirements of patients. At baseline examination, the average steroid (dexamethasone) dose was 21 mg 1 day prior to implantation, 18 mg on Day 7, and 7 mg on Day 49.

Wafer Dissolution

The opportunity was taken at autopsy or at reoperation to examine resection sites for the presence of wafer remnants. Small, amorphous, semi-solid fragments of polymer were found at reoperation in Group 2 patients. One patient from Group 3, who died 6 weeks after wafer implantation, was found at autopsy to have round, white, smooth discs, similar in size but flexible and less brittle than the original wafers. Three other Group 3 patients, who underwent autopsy or reoperation 13 to 23 weeks after implantation, had persistent discs *in situ*. No BCNU was detected in any of the remnants obtained nor were polyanhydride bonds present, suggesting that the material was a degraded remnant of the BCNU polyanhydride complex. Subsequent review did not show any correlation between the persistence of polymer remnants and the occurrence of specific neurological signs in individual patients.

Postmortem Examination

Four brains were examined postmortem. At least one whole-brain histological section taken through the tumor bed was prepared from each case. The cause of death in each of the four patients could be attributed to a massive recurrent neoplasm which, in all cases, extended into the opposite cerebral hemisphere via the corpus callosum. In three of the patients, a gliosarcoma was present. This was only a focal finding in two of the lesions but was of sufficient size to exert considerable mass effect in the third case. There was extensive necrosis throughout much of all four neoplasms; however, this did not appear excessive for these malignant neoplasms with their history of radiotherapy. Neither parenchymal necrosis nor vascular fibrinoid necrosis was noted in the surrounding nontumor-bearing brain.

Discussion

Drug Delivery to the Brain

We have demonstrated that a biodegradable polymer implant can be used safely to release a therapeutic drug to treat human brain tumors. This approach goes a step beyond previous attempts to increase exposure of such tumors to BCNU. Examples of these previous approaches include high-dose intravenous BCNU with bone marrow salvage,[24] BCNU infusion after osmotic disruption of the blood-brain barrier,[29] perioperative use of BCNU,[8] and selective intra-arterial infusion of BCNU to the affected hemisphere.[18] Although BCNU is lipid-soluble and readily crosses the blood-brain barrier, it rapidly decomposes in the bloodstream ($T_{\frac{1}{2}}$ 15 minutes), which detracts from the usefulness of these methods. Direct comparison of intracranial and intraperitoneal BCNU polymer implants shows a 113-fold increase in brain exposure to BCNU by using a brain implant.[34]

Wolpert, *et al.*,[33] and Harbaugh, *et al.*,[15] delivered BCNU directly into the tumor resection cavity by a catheter system. This approach is limited by the rapid decomposition of BCNU in aqueous solution. The polyanhydride polymer used for the BCNU wafers is sufficiently hydrophobic to protect the BCNU until it is released into the tumor environment.[14]

Systemic Exposure

A major advantage of local interstitial chemotherapy is the ability to avoid dose-limiting systemic side effects. In this study, patients treated with eight wafers received intracranial doses of about 30 mg, 60 mg, or 100 mg of BCNU, depending on the treatment group. By comparison, the standard single intravenous dose of BCNU is 200 mg. The systemic doses cause enough toxicity so

that long recovery intervals are needed between courses, thus limiting the usefulness of systemic treatment. No systemic side effects were attributed to the BCNU wafers nor were there any toxic effects on blood cells, electrolytes, or other organs. This high degree of tolerance is remarkable considering the relatively large amounts of drug released directly into the tumor and surrounding central nervous system.

Local Effects in the Brain

Some local effects of the drug were observed. A variable enhancing effect on CT was found in 13 of the 21 patients. The enhancement was similar to that observed with other local treatments (interstitial radiation[32] and intratumoral IL-2[2]) and hyperthermia,[31] where a central zone of nonenhancing lucency is located within a ring-shaped area of irregular enhancement. Despite enhancement, mass effect was minimal and spontaneous resolution was observed in some patients about 3 months after surgery. Not surprisingly, local tumor destruction was associated with some localized tissue necrosis; therefore, some patients underwent reoperation because of increasing mass effect (as demonstrated by deterioration in neurological function requiring increasing corticosteroids and by increasing enhancement on CT scanning or MR imaging). Mostly necrotic material was found at reoperation at distances of up to 1 cm from the tumor resection surface. With removal of the necrotic material, the neurological condition of the patients generally improved.

Survival Times

Survival of patients in the groups with a lower BCNU concentration appeared to be greater than for patients in the highest dose group (Group 3), although definitive conclusions cannot be drawn regarding treatment efficacy because of the small number of patients, differences in tumor type, and lack of cohort control. Harsh, *et al.*,[16] and Ammirati, *et al.*,[1] have reported the median survival time of patients following reoperation for malignant glioma as 36 weeks. In the present study, eight of 10 patients in the first two treatment groups survived beyond 36 weeks; the mean survival times at the cutoff date were 65 and 64 weeks, respectively. In Group 3, which consisted entirely of patients with glioblastomas, only four of 11 patients survived longer than 36 weeks. The overall mean survival time was 48 weeks from implantation and 94 weeks from the original operation. The overall median survival time was 46 weeks from implantation and 87 weeks from initial operation.

Conclusions

This is the first study in a clinical program that explores the intracranial delivery of a chemotherapeutic agent via a biodegradable carrier system. The results show that this novel approach to the treatment of brain tumors is feasible and safe. A placebo-controlled randomized clinical trial is currently under way at 23 centers in the United States and Canada to determine the effect on survival of supplying 3.85% BCNU in biodegradable polymers as treatment for recurrent malignant glioma. Because the treatment is so well tolerated, numerous agents may be incorporated into the polymers. This approach may prove to be a therapeutic advance for a variety of central nervous system diseases.

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